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(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING COCAINE DEPENDENCY

(57) Abstract

Anticonvulsant derivatives useful in treating cocaine dependency are disclosed.

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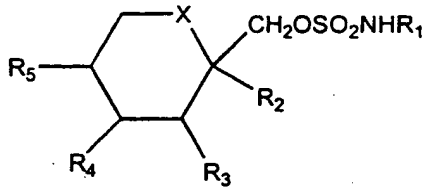
ANTICONVULSANT DERIVATIVES USEFUL IN TREATING COCAINE DEPENDENCY

BACKGROUND OF THE INVENTION

Compounds of Formula I:



I

are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. Bioorganic & Medicinal Chemistry Letters 3, 2653-2656, 1993). These compounds are covered by US Patent No.4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., Epilepsia 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, Epilepsia 36 (S4) 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in approximately twenty countries including the United States, and applications for regulatory approval are presently pending in several additional countries throughout the world.

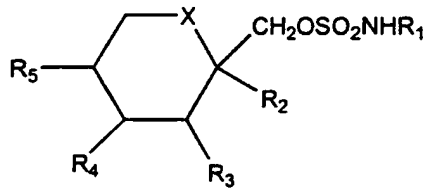
Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., Epilepsia 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T.

KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

Preclinical studies have revealed an apparent pharmacological property of topiramate that suggests it will be effective in treating cocaine abuse and dependence.

DISCLOSURE OF THE INVENTION

Accordingly, it has been found that compounds of the following formula I:



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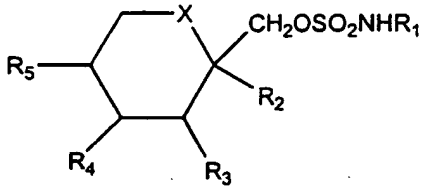
wherein X is O or CH_2, and R1, R2, R3, R4 and R5 are as defined hereinafter are useful in treating cocaine abuse and dependency.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

The sulfamates of the invention are of the following formula (I):



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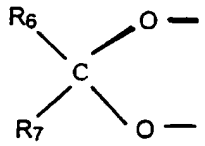
wherein

X is CH_2 or oxygen;

R_1 is hydrogen or C_1-C_4 alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or C_1-C_3 alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following

formula (II):

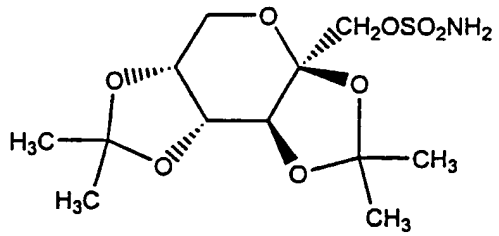


wherein
R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl, iso-propyl, *n*-propyl, *n*-butyl, isobutyl, *sec*-butyl and *t*-butyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R_2, R_3, R_4, R_5, R_6 and R_7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and *n*-propyl. When X is CH_2, R_4 and R_5 may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R_4 and R_5 are defined by the alkatrienyl group =C-CH=CH-CH=.

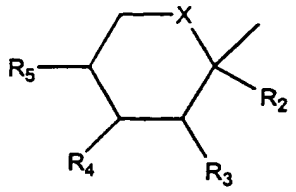
A particular group of compounds of formula (I) is that wherein X is oxygen and both R_2 and R_3 and R_4 and R_5 together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R_6 and R_7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R_2 and R_3 are hydrogen.

A particularly preferred compound for use in the methods of the present invention is 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate, known as topiramate. Topiramate has the following structural formula



The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR_1$ in the presence of a base such as potassium a-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



III

(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl.

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of abut 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula RCH_2OSO2N_3 as described by M. Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3 and R_4 and R_5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene

chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Volaa 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the processes disclosed in U.S. Patent Nos. 4,513,006, 5,387,700 and 5,387,700, all of which are incorporated herein by reference. More particularly, topiramate may be prepared following the process described in Examples 1 to 3 of U.S. 5,387,700.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R_2, R_3, R_4 and R_5 on the 6-membered ring. Preferably, the oxygen of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

The pharmacological properties of cocaine that cause it to be a drug of abuse and to induce a state of dependency in cocaine addicts is complex and not fully understood, but abundant evidence exists indicating that a modulation of dopaminergic neural pathways in a prominent factor (Klein, M. Research issues related to development of

medications for treatment of cocaine addiction. Ann. N. Y. Acad. Sci. 844, 75-91, 1998). Recent electrophysiological studies on the effects of topiramate on the physiological activity of neurons indicate the topiramate indirectly modulates the ability of the enzyme protein kinase A (PKA or cyclicAMP-dependent protein kinase) to phosphorylate some ligand activated ion channel proteins in the plasma membrane of neurons. Computer modeling studies demonstrate that topiramate can bind to the site on these ion channel proteins where PKA attaches the phosphate moiety. The amino acid sequence at which topiramate appears to bind to the ion channel proteins is RRXS, whrere R is arginine, S is serine and X is a neutral amino acid including, but not limited to, glutamine, asparagine or alanine. Several dopamine receptors and transporters are known to be phosphorylated by PKA [Zamanillo, D., Casanova, E., Alonso-Llamazares, A., Ovalle, S., Chinchetru, M. A., Calvo, P. Identification of a cyclic adenosine 3',5'-monophosphate-dependent protein kinase phosphorylation site in the carboxy terminal tail of human D1 dopamine receptor. Neurosci. Lett. 188(3), 183-186, 1995; Pristupa, Z. B., McConkey, F., Liu, F., Man, H. Y., Lee, F. J. S., Wang, Y. T.; Niznik, H. B. Protein kinase-mediated bidirectional trafficking and functional regulation of the human dopamine transporter. Synapse (N. Y.) 30(1), 79-87, 1998]. Topiramate, by virtue of binding to these phosphorylation sites should allosterically modulate the biological activity of these dopamine receptors and transporters and prevent PKA from phosphorylating these regulatory sites. The likely consequence of this biological activity is that the functional state of the dopaminergic mediate neural pathways will be reduced during periods of high activity, as occurs acutely after cocaine ingestion, and may be enhanced during periods of abnormally low activity, as occurs during cocaine withdrawal [Self, D. W., Genova, L. M., Hope, B. T., Barnhart, W. J., Spencer, J. J., Nestler, E. J., Involvement of cAMP-dependent protein kinase in the nucleus accumbens in cocaine self-administration and relapse of cocaine-seeking behavior. J. Neurosci. (1998), 18(5), 1848-1859].

For treating cocaine dependency, a compound of formula (I) may be employed at a daily dosage in the range of about 15 mg to about 1000 mg, preferably, about 50 mg to about 500 mg, most preferably, about 100 mg to about 250 mg for an average adult human, administered one to four times per day, preferably, one to two times per day. A unit dose typically contains about 15 to about 250 mg of the active ingredient.

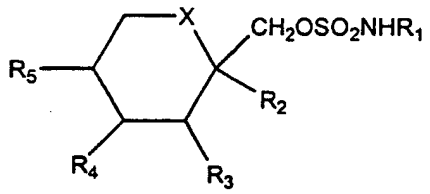
Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 15 to about 250 mg of the active ingredient.

WHAT IS CLAIMED IS:

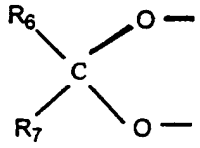
1. A method for treating cocaine dependency in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of the formula I:



I

wherein

X is CH_2 or oxygen;
R_1 is hydrogen or C_1-C_4 alkyl; and
R_2, R_3, R_4 and R_5 are independently hydrogen or C_1-C_3 alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



wherein R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl or
R_6 and R_7 together with the carbon to which they are attached are joined to form a cyclopentyl or cyclohexyl ring.

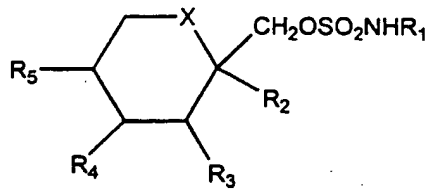
2. The method of claim 1, wherein the compound of formula I is topiramate.

3. The method of claim 1, wherein the total daily therapeutically effective amount is of from about 15 mg to about 500 mg.

4. The method of claim 1, wherein the unit dose amount is of from about 15 mg to about 250 mg

5. The method of claim 1, wherein the compound is administered as a pharmaceutical composition.

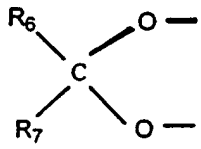
6. A method of decreasing cocaine use in a subject suffering from cocaine dependency comprising administering to the subject a therapeutically effective amount of a compound of the formula I:



I

wherein

X is CH_2 or oxygen;
R_1 is hydrogen or C_1-C_4 alkyl; and
R_2, R_3, R_4 and R_5 are independently hydrogen or C_1-C_3 alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



wherein R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl or
R_6 and R_7 together with the carbon to which they are attached are joined to form a cyclopentyl or cyclohexyl ring.

7. The method of claim 6, wherein the compound of formula I is topiramate.

8. The method of claim 6, wherein the total daily therapeutically effective amount is of from about 15 mg to about 500 mg.

9. The method of claim 6, wherein the unit dose amount is of from about 15 mg to about 250 mg.

10. The method of claim 6, wherein the compound is administered as a pharmaceutical composition.